BJU International (2002), 89, 710–713

The correlation between pretreatment serum hormone levels and treatment outcome for patients with prostatic cancer and bony metastasis

S.S. CHEN, K.-K. CHEN, A.T.L. LIN, Y.-H. CHANG, H.H. WU and L.S. CHANG

Division of Urology, Department of Surgery, Taipei Veterans General Hospital, Shu-tien Urological Research Center, and Department of Urology, National Yang-Ming University, School of Medicine, Taipei Municipal Jen-Ai Hospital, Taipei, Taiwan, Republic of China

Objective To evaluate whether pretreatment serum hormone levels are a prognostic factor for prostatic cancer with bony metastasis under hormonal treatment.

Patients and methods Between 1980 and 1994, 96 patients with prostate cancer and bony metastasis were included for an evaluation by a retrospective review of their charts. All 96 had received hormonal treatment after a diagnosis of metastatic prostatic carcinoma. Serum testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin were assessed before treatment. The patients were divided into two groups according to their response during the follow-up. Group 1 (good response) had no change or resolution of metastatic lesion(s) on the bone scan and a declining prostate-specific antigen (PSA) level. Group 2 had increased PSA or progression of metastatic lesion(s) on the bone scan. Tumours were graded as low (2–4), intermediate (5–7) and high (8–10) using the Gleason score.

Results There were 43 patients in group 1 and 53 in group 2; the overall mean (SD) age was 72.5 (6.8) years and the follow-up 29.5 (0.5) months. The respective mean (SD) levels of testosterone, LH, FSH and prolactin before treatment were 4.6 (1.6) ng/mL, 20.2 (13.3) mIU/mL, 19.6 (18.6) mIU/mL and 20.7 (12.1) ng/mL in group 1, and 2.6 (1.0) ng/mL, 27.3 (11.0) mIU/mL, 27.1 (9.8) mIU/mL and 41.3 (28.4) ng/mL in group 2. The level of testosterone was significantly higher in group 1 than in group 2, while LH, FSH and prolactin were significantly lower in group 1 than in group 2. When stratified by tumour grade, patients in group 1 still had significantly higher pretreatment testosterone and lower LH, FSH and prolactin than those in group 2.

Conclusion Higher testosterone and lower LH, FSH and prolactin levels were good prognostic factors for patients with metastatic prostatic cancer under hormonal treatment, irrespective of tumour grading.

Keywords prostatic carcinoma, testosterone, prolactin, LH, FSH, prognosis

Introduction

Huggins and Hodges [1] suggested that the growth of prostatic carcinoma is stimulated by androgen and inhibited by oestrogen; reducing the androgen level resulted in a good response in most patients with prostatic carcinoma [2]. Prognostic factors for prostatic cancer, including clinical, endocrinological and pathological factors, have been reported previously [2–11]. Reiter *et al.* [12] showed that the involvement of prolactin, growth hormone and LH is an issue that needs to be addressed. Harper *et al.* [13] reported that low testosterone and high LH are poor prognostic factors for prostatic carcinoma, but Houghton and Jacobi [14] reported no correlation. Therefore, the role of pretreatment plasma testosterone levels in prostatic cancer remains controversial.

As for prolactin, Morales and Nickel [15] stated that persistent hyperprolactinaemia carries an ominous prognosis for patients with prostatic cancer under hormonal treatment, and Adlercreutz *et al.* [7] showed that prolactin levels were ≈30% lower in patients with prostatic cancer with a good response to hormonal treatment than in those with a poor prognosis.

To evaluate the correlation between pretreatment hormones, including testosterone, LH, FSH and prolactin, and the prognosis for prostatic carcinoma with bony metastasis under hormonal therapy, we conducted a retrospective study.

Accepted for publication 30 January 2002

Patients and methods

From 1980 to 1994, 96 patients with prostatic cancer and bony metastasis under hormonal treatment were included in an evaluation. Prostatic cancer was confirmed by TRUS and biopsy or TURP, and bony metastasis confirmed by whole-body bone scintigraphy. Patients who were not regularly followed up or who had suspicious lesions on bone scans were excluded. Serum testosterone, LH, FSH, prolactin and PSA were evaluated in all 96 patients before treatment by RIA (normal ranges: testosterone 3–10 ng/mL, LH 1–15 mIU/mL, FSH 1–15 mIU/mL, prolactin 2.0–14.7 ng/mL and PSA <4 ng/mL). These patients were a small but unselected group of the total number of patients with prostate cancer treated over this period. Some staff physicians measured the levels of the relevant hormones before hormonal treatment because they were interested in this issue (not because these investigations were specifically indicated in these patients), although these hormones are not routinely assessed in patients with prostate cancer at our hospital. In particular, none of the patients had testicular atrophy at presentation. Of the 96 patients, 77 underwent orchidectomy and 19 were treated with DES therapy, but no patient received total androgen blockade initially. The castrate level of testosterone (<0.2 ng/mL or 5% of the pretreatment level) was confirmed for all 96 patients under hormonal treatment during the follow-up [16].

Tumours were graded as low (2–4), intermediate (5–7) and high (8–10) using the Gleason score. The patients were divided into two groups according to their response after hormonal treatment. The treatment outcome was defined as follows. Group 1 attained a PSA nadir after hormonal treatment of <4 ng/mL or an undetectable level with no increase in PSA during the follow-up; and resolution or no change of previous metastatic lesion(s), and no new metastatic lesion(s) on bone scintigraphy during the follow-up. Group 2 had no PSA nadir after hormonal treatment or had increased PSA during the follow-up; and new metastatic lesion(s) or progression of previous lesion(s) during the follow-up. Thus group 1 comprised those patients who had a good response after hormonal treatment and group 2 those who had a poor response.

The Mann–Whitney *U*-test and Kruskal–Wallis test were used for the statistical analysis, with $P < 0.05$ considered to indicate statistical significance.

Results

The mean (SD) age of the patients was 72.5 (6.8) years and the mean follow-up 29.5 (10.5) months. There were 43 patients (45%) in group 1 and 53 (55%) in group 2. The mortality rate at 18 months was 19% in group 1 and 83% in group 2. The distribution of grade overall and within the groups is shown in Table 1. Higher tumour

Table 1 Pretreatment serum hormone and PSA levels in patients with prostatic cancer

	Mean (SD)				
Category (n)	*Testosterone*	*LH*	*FSH*	*Prolactin*	*PSA*
Group 1 (43)	4.6 (1.6)	20.2 (13.3)	19.6 (18.6)	20.7 (12.1)	143.1 (305.9)
Group 2 (53)	2.6 (1.0)	27.3 (11.0)	27.1 (9.8)	41.3 (28.4)	130.4 (228.4)
P	<0.001	<0.001	<0.001	<0.001	0.097
Tumour grade					
Low (15)	4.2 (1.9)	20.7 (10.0)	18.5 (8 6)	36.4 (48.9)	95.3 (154.5)
Intermediate (53)	3.4 (1.7)	24.6 (14.4)	24.8 (17.7)	31.3 (18.0)	169.4 (335.7)
High (28)	3.2 (1.3)	24.9 (9.6)	24.6 (10.7)	31.4 (16.7)	94.9 (109.1)
P	0.169	0.144	0.109	0.103	0.793
Patients with:					
low-grade					
Group 1 (10)	5.2 (1.5)	15.8 (4.0)	14.5 (6.1)	14.1 (7.6)	101.4 (190.2)
Group 2 (5)	2.3 (0.8)	30.5 (11.7)	26.5 (7.5)	80.8 (67.3)	83.1 (43.2)
P	0.002	0.014	0.007	0.020	0.197
intermediate					
Group 1 (24)	4.4 (2.6)	22.7 (17 2)	23.5 (24.0)	24.7 (13.6)	166.4 (379.1)
Group 2 (29)	2.6 (1.0)	26.2 (11 7)	25.8 (10.4)	36.7 (19.5)	171.8 (302.0)
P	<0.001	0.023	0.012	0.003	0.191
high-grade					
Group 1 (9)	4.3 (0.8)	18.3 (4.1)	14 8 (4.8)	17.5 (7.7)	127.5 (182.8)
Group 2 (19)	2.6 (1.2)	28.0 (10)	29 2 (9.5)	37.9 (15.8)	79.5 (47.3)
P	0.001	0.002	<0.001	<0.001	0.980

grades were associated with a poorer response under hormonal treatment.

Pretreatment hormone and PSA levels of all patients in the two groups and for different tumour grades are also shown in Table 1. Patients in group 1 had significantly higher testosterone and lower LH, FSH and prolactin levels than those in group 2, but there were no significant differences in hormone levels among the three tumour grades. The hormone levels and PSA in the two groups stratified by tumour grading are also shown in Table 1; the testosterone levels were significantly higher and LH, FSH and prolactin levels lower in patients in group 1 than in group 2, after stratifying for tumour grade. There was no significant difference in PSA between the two groups or with tumour grade (Table 1).

Discussion

Evaluating the clinical, pathological and hormonal factors as prognostic indicators in prostatic carcinoma should provide a better understanding of the mechanism affecting disease progression and the interrelationship of the endocrine system with tumour pathology and stage [13]. That a higher tumour grade leads to a poor prognosis is obvious [10,17]. Harper *et al.* [13] suggested that there is no clear relationship between hormone levels (e.g. testosterone, prolactin, growth hormone and gonadotrophin) and tumour grade. This was supported by the present study. To reduce the bias of tumour grading, the grades were stratified for comparison. There was no significant difference in pretreatment PSA levels with tumour grade and response because the SD was large.

The PSA nadir is an important indicator of response to hormonal treatment. Stamey *et al.* [18] stated that 22% of patients with D2 prostatic cancer had reached their PSA nadir under hormonal treatment. Miller *et al.* [19] found that patients who reached a PSA nadir of <4 ng/mL had a significantly longer remission than those who failed. Therefore, in the present study, we used the PSA nadir as a factor for evaluating treatment outcome.

Sex steroids, particularly androgen, are important in the development of prostatic carcinoma, but the mechanism remains unknown. Androgens are important for growth and maintenance of the prostate, for stimulating the proliferation of human prostate cancer *in vitro* and for producing prostate cancer in rodents [20,21]. Gann *et al.* [22] suggested that high testosterone and low sex hormone-binding globulin are associated with a higher risk of prostate cancer. Vermeulen [23] showed that testosterone would not stimulate the development of subclinical prostatic carcinoma to become a clinical carcinoma. A low plasma testosterone level associated with a poor treatment response for prostatic carcinoma was reported by several groups [13,24,25], but not by others [14]. Young and Kent [24] reported that low testosterone might be connected with chronic disease status, and Harper *et al.* [13] speculated that low testosterone results in the growth of more androgen-independent carcinoma cells, which show a poor response to hormonal treatment. A similar result was provided by the present study for testosterone. However, all the present patients had prostatic cancer and bony metastasis, which differs from the situation reported by Harper *et al.* Indeed, if a patient already has testosterone levels in the castrate range, the prostate cancer will progress despite therapeutic androgen deprivation. In the present study, no patient had a castrate range of testosterone or atrophy of the testis before hormonal treatment. However, the possibility cannot be discounted that tumours developing in a low but higher than castrate level of serum testosterone might become relatively less hormone-sensitive.

The role of prolactin in prostatic cancer is unclear. High plasma prolactin level have been reported to carry a poor prognosis [26] and the proliferation of androgen-independent human prostate cell line can be significantly modulated by prolactin [27]. Rana *et al.* [28] speculated that the combined maximum suppression of androgen and prolactin offers a significant improvement in response for advanced prostatic cancer. In the present study, prolactin levels were significantly lower in group 1 than group 2.

Harper *et al.* [13] suggested that a high LH is a poor prognostic factor for prostatic cancer, with or without metastasis. In the present study, LH and FSH were significantly higher in group 2.

In conclusion, higher serum testosterone and lower LH, FSH and prolactin levels were good prognostic factors for patients with metastatic prostatic cancer under hormonal treatment, irrespective of tumour grading.

References

1 Huggins C, Hodges CV. Studies on prostatic cancer, the effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res* 1941; 1: 293

2 Scott WW, Menon M, Walsh PC. Hormonal therapy of prostatic cancer. *Cancer* 1980; **45** (Suppl. 7): 1929

3 Byar DP, Huse R, Bouillar JC III, the Veterans Administration Co-operative Urological Research Group (VACURG). An exponential model relating censored survival data and concomitant information for prostatic cancer patients. *J Cancer Inst* 1974; 2: 321–6

4 Berry WR, Laszlo J, Cox E, Walker A, Paulson D. Prognostic factors in metastatic and hormonally unresponsive carcinoma of the prostate. *Cancer* 1979; **44**: 763–75

5 Byar DP, Corle DK. Analysis of prognostic factors for prostatic cancer in the VACURG studies. In Denis L, Murphy GR, Prout GR, Schroder F eds. *Controlled Clinical Trials in Urological Oncology*. New York: Raven Press, 1984: 147–69
6 Harper ME, Pierrepoint CG, Griffiths K. Carcinoma of the prostate: relationship of pretreatment hormone levels to survival. *Eur J Cancer Clin Oncol* 1984; 20: 477–82
7 Aldercreutz H, Rannikko S, Kairento AL, Karonen SL. Hormone patterns in prostatic cancer II. Correlation with primary response to endocrine treatment. *Acta Endocrin* 1981; 98: 634–40
8 Trachtenberg J, Walsh PC. Correlation of prostatic nuclear androgen receptor content with duration of response and survival following hormonal therapy in advanced prostatic cancer. *J Urol* 1982; 127: 466–71
9 Wilson DW, Harper ME, Jensen HM *et al.* A prognostic index for the clinical management of patients with advanced prostatic cancer: a British Prostate Study Group Investigation. *Prostate* 1985; 7: 131–41
10 Gleason DF, Mellinger GT, the VACURG. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. *J Urol* 1974; 111: 58–64
11 Byar DP, Mostifi FK, the VACURG. Carcinoma of the prostate – prognostic features in 20% of radical prostatectomies. *Cancer* 1972; 30: 5–15
12 Reiter E, Hennuy B, Bruyninx M *et al.* Effects of pituitary hormones on the prostate. *Prostate* 1999; 38: 159–65
13 Harper ME, Wilson DW, Jensen HM, Pierrepoint CG, Griffiths K. Steroid hormone concentrations in relation to patient prognosis and prostate tumor grade. *J Urol* 1987; 27: 521–4
14 Houghton AL, Jacobi HS. Advanced cancer of the prostate – does pretreatment Leydig cell function determine the response to therapy? *Postgrad Med J* 1978; 34: 261–4
15 Morales A, Nickel JC. Clinical relevance of plasma testosterone and prolactin changes in advanced cancer of prostate treated with diethylstilbestrol or estramustine phosphate. *Urology* 1985; 26: 477–81
16 Lin BJ, Chen KK, Chen MT, Chang LS. The time for serum testosterone to reach castrate level after bilateral orchiectomy or oral estrogen in the management of metastatic prostatic cancer. *Urology* 1994; 43: 834–7
17 Byar DP, Mostifi FK. Cancer of the prostate in men less than 50 years old. An analysis of 51 cases. *J Urol* 1969; 102: 726–33
18 Stamey TA, Kabalin JN, Ferrari M *et al.* Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. IV Anti-androgen treated patients *J Urol* 1989; 141 1088–90
19 Miller JI, Ahman FR, Drach GW *et al.* The clinical usefulness of serum PSA after hormonal therapy of metastatic prostate cancer. *J Urol* 1992; 147 956–61
20 Hederson BE, Ross RK, Pike MC, Casgrande JT. Endogenous hormones as a major factor in human cancer *Cancer Res* 1982; 42: 3232–9
21 Noble RL. The development of prostatic adenocarcinoma in Nb rats following prolonged sex hormone administration *Cancer Res* 1977; 37: 1929–033
22 Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Ins* 1996; 16: 1118–26
23 Vermeulen A. Andropause. *Maturitas* 2000; 34: 5–15
24 Young HH, Kent JR. Plasma testosterone levels in patients with prostatic carcinoma before and after treatment. *J Urol* 1968; 99: 788–92
25 Robinson MRG, Thomas BS. Effect of hormonal therapy on plasma testosterone levels in prostatic cancer. *Br Med J* 1971; 4: 391–4
26 Mee AD, Khan O, Mashiter K. High serum prolactin associated with poor prognosis in carcinoma of the prostate. *Br J Urol* 1984; 56: 698–701
27 Jassen T, Darro F, Petein M *et al. In vitro* characterization of prolactin-induced effects on proliferation in the neoplastic LNCap, DU145, and PC3 models of the human prostate. *Cancer* 1996; 77: 144–9
28 Rana A, Habib P, Halliday P *et al.* A case for synchronous reduction of testicular androgen and prolactin for the treatment of advanced carcinoma of the prostate. *Eur J Cancer* 1995; 6: 871–5

Authors

S.S. Chen, MD, PhD, Urology Specialist.
K.K. Chen, MD, PhD, Professor and chief of Urology.
A.T.L. Lin, MD, PhD, Professor of Urology.
Y.H. Chang, MD, PhD, Associate Professor of Urology.
H.H. Wu, MD, PhD, Associate Professor of Urology.
L.S. Chang, MD, Urologist, Professor of Urology.
Correspondence: K.-K. Chen, Division of Urology, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan 112, Republic of China.
e-mail: kkchen@vghtpe.gov.tw